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Colleen Coyne
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Philippe Collas et al.	Art Unit:	1632
Serial No.:	10/032,191	Examiner:	Woitach, Joseph T.
Filed:	December 21, 2001	Customer No.:	21559
Title:	METHODS FOR CLONING MAMMALS USING REPROGRAMMED DONOR CHROMATIN OR DONOR CELLS		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. JAMES M. ROBL UNDER 37 C.F.R. ∋ 1.132
TRAVERSING GROUNDS OF REJECTION

Under 37 C.F.R. ∋ 1.132 and regarding the rejection of claims 1, 4-15, and 43-53, I declare:

1. I am a co-inventor of the subject matter that is described and claimed in the above-captioned patent application.

2. I hold a Ph.D. from the University of Illinois and, prior to founding the company, Hematech LLC, was a professor at the University of Massachusetts for 15 years, where my work focused on mammalian cloning and genetic modification. In January 1998, I and my laboratory were the first scientists to clone a transgenic cow from genetically modified somatic cells.

3. I have considered the Patent Office's concerns regarding the workability of the present invention. On this issue, I first point out that the cell cycle is typically divided into two general stages: mitosis and interphase. During mitosis, chromatin condensation and nuclear envelope breakdown occur, the events that appear to facilitate the enhanced efficiency of our cloning method. Cell populations isolated in mitosis, and without further isolation based on cell stage, reproducibly trigger those events of chromatin condensation and nuclear envelope breakdown and have been used for the successful cloning of a variety of mammalian species.

4. In my laboratory at Hematech LLC, mitotic cells are routinely isolated by the technique generally described in the present specification at page 36, lines 23-26 and extracts prepared as generally described in the specification at page 36, line 28 – page 37, line 27. Such extract preparation has been carried out at least 75 independent times in my laboratory and is currently carried out by technician level scientists. When tested, these extracts are found to reproducibly trigger chromatin condensation and nuclear envelope breakdown. Extracts at Hematech are typically tested by visual assessment for chromatin condensation as described in the specification, for example, at page 30, lines 29-30. In these tests, we have determined that essentially 100% of the mitotic extracts assayed are functional.

5. In addition, these mitotic cell extracts reproducibly result in the cloning of desired mammals. At Hematech, this technique has been used to clone at least 25,000 bovine embryos and has been used by others to clone mammals of species as diverse as pigs and cats. In each case, mitotic cell extracts have been successfully utilized in these endeavors.

6. I further note that our technique has allowed for mammalian cloning across a broad range of cell types and species. In experiments carried out by my laboratory or others, functional mitotic extracts have been generated from both primary and cultured cells, in particular, primary bovine fetal fibroblasts as well as cultured Madin Darby

bovine kidney cells and cultured Madin Darby canine kidney cells. Extracts have also been generated and used successfully from a broad range of species that include bovines, canines, and humans. All of these extracts were shown to trigger chromatin condensation and nuclear envelope breakdown.

7. Furthermore, these extracts triggered these events in an apprarently non-species-specific manner. Bovine mitotic extracts have been demonstrated to trigger chromatin condensation and nuclear envelope breakdown in bovine fibroblasts, bovine trophectodermal cells, and bovine placental cells, as well as porcine fetal fibroblasts, canine fibroblasts, and monkey fibroblasts. These results indicate that a mitotic extract from one species can be used to clone other species and that this is true with respect to species as diverse as cows, pigs, dogs, and monkeys.

8. Consistent with this broad range of cell types and species amenable to our cloning approach, the technique has been used by my laboratory or others to successfully generate cloned fetuses from cows, pigs, and cats, and for research to clone monkeys.

9. Due to its success, our technique has received widespread recognition in the scientific and popular press. For example, the success of the present technique has been published in the peer-reviewed journals, *Nature Genetics* and *Biology of Reproduction.* In addition, the use of our technique to clone domestic cats has been reported on television and the internet by MSNBC.

10. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of thc application or any patents issued thereon.

10 Oct 2005
Date

Dr. James M. Robl

to: Jim Barton

CONFIDENTIAL

Title of Invention: Reprogramming of somatic cell nuclei in vitro for use in nuclear transplantation

Please check campus of lead Principal Investigator Amherst ☑ Boston ☐ Dartmouth ☐ Lowell ☐ UMMC ☐

To the Inventor(s):

The business of a university is the gathering and dissemination of knowledge. Making an invention and putting it to use in the service of the public is a thoroughly valid mode of accomplishing this objective.

Accordingly, the University encourages the inventive process; and within the limits of financial practicality, can often provide advice and assistance in bringing inventions to the point of public use.

In the sense used here, an "invention" has a presumed commercial use and value. The following indicates the preferred time to file a disclosure with CVIP.

- ***Disclose to CVIP first; publish later:*** Disclosing your invention to CVIP by no means proscribes publication; on the other hand, premature publication can have disastrous consequences, both legal and tactical, upon an effort to commercialize it by precluding the availability of patent protection in most countries.
- ***Disclose as soon as the invention is clearly conceptualized.*** It is not necessary to wait until the invention is reduced to practice, and filing early may be beneficial, particularly when other groups are filing related patent applications.
- ***Consult with CVIP specialists:*** CVIP specialists can assist you with such questions as determining inventorship, procedures when more than one institution is involved and protecting patentable inventions from improper public disclosure.

If you <u>think</u> you have made an invention, but you are not sure, then say so in your disclosure. Similarly, if you are uncertain as to whether your invention has commercial merit, say so. CVIP can assist you in making such determinations. This form should be considered as a guide to assist in the invention disclosure procedure as required by the University's Intellectual Property Policy.

1. BACKGROUND

In order for patent counsel to determine the patentability of this invention, it will be necessary to compare it to existing technology (referred to as "prior art"). This section should provide information to aid in that evaluation. Please identify and provide references to the prior art by patent number or journal article identification.

Two kinds of prior art are applicable. The first is the field of nuclear transplantation and the second is work that has been done using cell-free cytoplasmic extracts for studying the control of the cell cycle.

The field of nuclear transplantation is well documented in UMass patent 5,945,577 and Infigen patent 6,011,197 and references contained within. All existing patents on nuclear transplantation use intact donor cells. Isolated donor nuclei have been used in the mouse for nuclear transplantation by Teru Wakayama (see attached references by Wakayama). These nuclei were injected into recipient oocytes immediately after rupturing the cell membrane. No attempt was made to reprogram the nuclei prior to injection into the oocyte.

A U.S. patent search using the term "cytoplasmic extract" gave no results for 1999-2000. Cytoplasmic extracts have been used for many years to study the regulation of the cell cycle and events associated with

changes in cell cycle phase. These extracts have been used to cause nuclei to condense into chromatin and decondense and form nuclei (see attached references).

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Inventor's Name & Title *(Please list Principal Investigator first and include all possible inventors)*	Department *(at time invention was made)*	Institution *(at time invention was made)*
1. Name: James M. Robl Title: Professor	Dept: Veterinary and Animal Science	Institution: University of Massachusetts
2. Name: Title:	Dept:	Institution:
3. Name: Title:	Dept:	Institution:
4. Name: Title:	Dept:	Institution:

Title of Invention: _Reprogramming Nuclear Function in Somatic Cell Cytoplasm_____